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A SOLUBLE MANGANESE CITRATE

AND SOME

COMPOUNDS OF MANGANESE WITH IRON

BY

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It is worthy of note that neither the British nor the German Pharmacopœia, in their latest editions, has adopted any salt of manganese or preparation made therefrom ; the United States Pharmacopœia recognises only manganese dioxide and manganese sulphate, whilst the French Codex, in addition to these, includes also the carbonate.

Although considerable diversity of opinion has existed, and apparently still exists, respecting the therapeutic value of manganese compounds, their wide distribution in organic nature, and their occurrence, together with iron, in the human body, in the blood and bile, would appear to render it probable that they play some part, however subordinate, in the vital processes of both animals and plants.

There can also be little doubt that the value of manganese compounds as medicinal agents depends to a considerable extent upon the form in which the element is administered. Manganese dioxide, for example, is still occasionally prescribed, notwithstanding its frequent impurity, its complete insolubility in

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water, and its very sparing solubility in dilute acids. With regard to the various salts of manganese at present known, several of which have been recommended from time to time for medicinal use, those which contain the element in organic combination appear to have been most favoured and to have become most largely employed. It furthermore seems probable that even among the organic salts those which are most freely soluble in water, and therefore most readily assimilated, will be found more effective than the less soluble ones.

These considerations have led to some experiments resulting in the preparation of such a soluble organic salt of manganese and some compounds with iron, the description of which is given in the present paper.

(1) SOLUBLE MANGANESE CITRATE.

Before describing the preparation and characters of this new soluble salt, it would seem desirable to refer briefly to the various citrates of manganese that have heretofore been prepared, for the purpose of presenting some comments thereon.

These salts, as recorded in Beilstein's 'Handbuch der organischen Chemie,' Bd. I., p. 838, have been studied chiefly by Kämmerer (Liebig's 'Annalen,' CXLVIII., 1868, p. 314), but the correctness of the composition assigned to some of them appears to be somewhat doubtful.

Kämmerer has stated that when manganous sulphate and sodium citrate are heated together in aqueous solution, in a certain degree of concentration, a crystalline, white precipitate is obtained, which, when dry, is slightly yellowish. The reaction has been represented by the following equation:—

$$2MnSO_4 + 2Na_3C_6H_5O_7 = MnH(C_6H_5O_7) + MnNa_2(C_6H_4O_7) + 2Na_2SO_4$$

The same salt is said to be obtained by heating manganous acetate with citric acid, or by heating together manganous sulphate, sodium acetate, and citric acid. Whereas Heldt had previously assigned to one of the above salts, obtained by the interaction of manganous carbonate and citric acid, the composition $MnHC_6H_5O_7 \cdot H_2O$, the salt obtained by Kämmerer was found to have the composition $2MnHC_6H_5O_7 \cdot H_2O$.

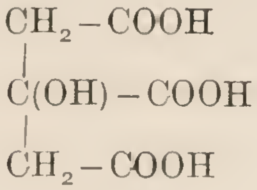
By heating together solutions of manganous acetate and citric acid, in the proportions of 1½ molecules of the former to 1 molecule of the latter, Kämmerer obtained the salt $Mn_3(C_6H_5O_7)_2 \cdot 9H_2O$ as a crystalline powder, and from the mother liquor of this salt, by evaporating on a water-bath and precipitating with alcohol, a salt was obtained to which he assigned the composition $Mn_5H_2(C_6H_4O_7)_3 \cdot 15H_2O$. From the above-mentioned mother liquor, by a slightly different procedure, he obtained a micro-crystalline salt, for which the composition $Mn_7H_2(C_6H_4O_7)_4 \cdot 18H_2O$ was given, and which was assumed to be formed by the following reaction :—

$$Mn_3(C_6H_5O_7)_2 + 2Mn_2(C_6H_4O_7) \cdot 18H_2O = Mn_7H_2(C_6H_4O_7)_4 \cdot 18H_2O.$$

From the liquid obtained by neutralising manganous carbonate in the cold with citric acid, Kämmerer furthermore obtained a salt which he considered to be a compound of a trimetallic and a tetrametallic salt, as represented by the following formula :—

$$Mn_3(C_6H_5O_7)_2 + Mn_2(C_6H_4O_7) \cdot 15H_2O = Mn_5H_2(C_6H_4O_7)_3 \cdot 15H_2O.$$

It will be observed that in the composition of several of the above-mentioned salts, as represented by Kämmerer, citric acid is regarded as tetrabasic. Although from the now well-known constitution of this acid,



$$\begin{array}{l} CH_2-COOH \\ | \\ C(OH)-COOH \\ | \\ CH_2-COOH \end{array}$$

it is seen to be tetratomic, it was recognised as tribasic by Liebig as long ago as 1838. It is therefore highly improbable that the composition of those salts can be correct which assumes the hydrogen of the alcoholic hydroxyl group to have been replaced by manganese.

Of the simple citrates of manganese two salts of different composition are found in commerce. Both of them occur in the form of a white powder, sparingly soluble in cold water. One of these, of German manufacture, was found by the writer to contain 17·8 per cent. of manganese, and is evidently an acid salt. A salt of the composition $MnHC_6H_5O_7\cdot 4H_2O$ would require 17·3 per cent. Mn. Another salt, of English manufacture, was found to be a normal manganese citrate, containing 23·58 per cent. Mn, and therefore corresponds to one of the salts first prepared by Kämmerer, namely, $Mn_3(C_6H_5O_7)_2\cdot 9H_2O$, which requires 23·3 per cent. Mn. These salts were assayed by simple ignition and weighing the residue as Mn_3O_4.

The last-mentioned salt serves as the basis for the preparation of a soluble manganese citrate. Although obtained by Kämmerer (*loc. cit.*) by heating a solution of manganous acetate with citric acid, the writer has prepared it by the action of citric acid upon manganous carbonate in the following calculated proportions:—

$$\underset{\substack{669\\(100)}}{\underline{3MnSO_4\cdot 4H_2O}} + \underset{\substack{858\\(128\cdot 2)}}{\underline{3Na_2CO_3\cdot 10H_2O}} = \underset{345}{\underline{3MnCO_3}}$$

$$\underset{345}{\underline{3MnCO_3}} + \underset{\substack{420\\(62\cdot 8)}}{\underline{2C_6H_8O_7\cdot H_2O}} + Aq = \underset{\substack{703\\(105)}}{\underline{Mn_3(C_6H_5O_7)_2\cdot 9H_2O}}$$

The proportions practically employed were as follows:—Manganese sulphate, cryst., 100 grammes; sodium carbonate, cryst., 140 grammes; citric acid, 62·8 grammes. The manganese sulphate and sodium carbonate are dissolved separately in a convenient quantity of water, with the aid of heat, and filtered. To the solution of manganese sulphate the sodium carbonate is added gradually, with constant stirring, and the precipitate, after being allowed to subside, is washed repeatedly by affusion and decantation with water until the washings afford not more than a slight reaction for sulphate. The moist manganese carbonate is then brought into a porcelain dish with a little water, the citric acid added, and the mixture heated on a water-bath for about half-an-hour, with occasional stirring. If the dry salt is desired, the product, which should form a somewhat thick mixture, is brought on a filter, washed with a little water, and dried at a gentle heat. It is thus obtained as a white crystalline powder, and the yield of the salt on a small scale is very nearly the theoretical. When assayed it afforded 23·17 per cent. Mn, as compared with 23·3 per cent. Mn calculated for $Mn_3(C_6H_5O_7)_2 \cdot 9H_2O$.

The Soluble Manganese Citrate was prepared as follows:— To the simple manganese citrate, obtained as above from 100 grammes manganese sulphate, while still moist and contained in a porcelain dish, 105 grammes of crystallised sodium citrate are added, and the mixture heated on a water-bath until complete solution is effected. The liquid is then diluted sufficiently to filter readily, and at once spread on glass plates, so that on drying it may be obtained in the form of scales. The salt in the state of solution oxidises readily and becomes brown, but in the dry state it is quite permanent when protected from the light. The amount of sodium citrate employed corresponds very nearly to the following molecular proportions:—

$$\underset{703.}{\underline{Mn_3(C_6H_5O_7)_2,9H_2O}} + \underset{714.}{\underline{2Na_3C_6H_5O_7,5^1/_2H_2O.}}$$

The salt forms handsome pearly scales, which are very freely soluble in water. Like other similar scale salts, it cannot be considered a definite chemical compound, and is subject to slight variations in composition according to the care exercised in its preparation, the thickness of the scales, and the temperature at which they are dried. Several determinations of the manganese have shown the latter to vary within the limits of about 12 to 13 per cent.

In a paper entitled "Recherches sur les citrates ammoniacaux," by Landrin (*Annales de chimie et de physique*, 1882, p. 233), the author, *loc. cit.* p. 252, describes an ammonio-citrate of manganese, "*citrate de manganèse biammoniacal*," which is stated to have been prepared as follows:—"*Si l'on fait réagir sur le citrate d'ammoniaque du carbonate de manganèse* (1 *éq d'acide citrique pour* 1 *éq de carbonate de manganèse*) *jusqu'à dissolution complète du carbonate, si l'on concentre la dissolution et si l'on fait cristalliser, on obtient un sel en croutes cristalline.*"

To this salt Landrin assigns the formula $C_{12}H_5O_{11}\cdot2AzH_4O$, MnO, which would correspond in the more modern notation to $Mn(NH_4)_4(C_6H_5O_7)_2$, and would contain theoretically 10·9 per cent. Mn. The author found 14·04 and 14·06 per cent. MnO=10·9 per cent. Mn. It therefore contains somewhat less manganese than the salt prepared by me, and is otherwise different in its character.

It is stated by Landrin that from solutions of the salt prepared by him the manganese is not precipitated by ammonia nor by potassa, incompletely precipitated by alkali carbonates, and *completely precipitated by ammonium sulphydrate*, in the latter respect having a character contrary to that indicated by Spiller for the action of alkali monosulphides on solutions of manganous salts in alkali citrates (*Journ. Chem. Society*, 1858, Vol. X., p. 110, and *Pharm. Journ.*, 1858, Vol. XVII., p. 282).

In the paper by Spiller he records the following observation :—"The protoxide of manganese is not precipitated by potassa, nor the carbonate by sodium carbonate, in presence of a soluble citrate. On exposure to the air the brown binoxide of manganese separates from the former only of these solutions. *Sulphide of manganese is not at all precipitated.*"

The soluble manganese citrate prepared by the writer is not precipitated by ammonia nor at once by potassa, although gradually forming with the latter a brown precipitate; it is either not precipitated by the alkali carbonates or gives but a slight turbidity. It is, however, at once and abundantly precipitated by ammonium sulphydrate, as also by potassium ferrocyanide.

In order to ascertain the cause of the above discrepancies, a solution was prepared in the manner and proportions indicated by Landrin. Although the manganese carbonate dissolved very slowly and incompletely in the solution of ammonium citrate, the solution obtained had the characters described, with the exception of not being precipitated by alkali carbonates. It was at once abundantly precipitated by ammonium sulphydrate, and also by potassium ferrocyanide.

Solutions were then prepared by dissolving respectively one molecular proportion of manganese carbonate with one of citric acid, and one molecule of manganese carbonate with two molecules of citric acid, and subsequently in both cases neutralising the excess of acid with ammonia. The former of these solutions was precipitated by ammonium sulphydrate, whereas the latter remained perfectly clear at first, and a precipitate was only gradually formed. Both of these solutions were only gradually precipitated by potassium ferrocyanide.

The apparent discrepancy between the observations of Spiller and Landrin is therefore easily explained by the fact that the precipitation of manganese by ammonium sulphydrate in the presence of alkali citrates depends simply upon the greater or less amount of the latter that may be contained in the solution.

(2) SOLUBLE IRON AND MANGANESE CITRATE.

A few years ago Dr. Da Costa, of Philadelphia, recommended the hypodermic use of iron, especially in those cases where a rapid action is needed, as after severe hæmorrhage, and for those people who have such delicate digestions that they cannot assimilate the iron when given by the mouth (*Lancet*, July 4, 1896, p. 227). The preparation employed for this form of administration was stated to be a ferrous-manganese citrate, which is stable and has not the irritating properties of many other compounds. The solution was prepared by dissolving the salt in hot distilled water in the proportion of one grain to five minims. A preparation, possibly designed to meet these special requirements, has been issued by a German manufacturer under the name of Ferro-Manganum Citricum, and is in the form of reddish-brown scales, freely soluble in water. A specimen of this salt, examined by the writer, contained the iron, however, not in the ferrous, as the name would imply, but in the ferric state. An analysis showed the presence of 15·3 per cent. of iron and 9·7 per cent. of manganese.

The salt now brought to notice differs somewhat from the above in its character, and in the percentages of iron and manganese. It is calculated to contain as nearly as possible two parts of metallic iron to one part of manganese, and these proportions may be attained within very close approximations in practice.

The method adopted for the preparation of this compound is as follows:—Simple manganese citrate is first prepared in the manner described under soluble manganese citrate. If, for example, 100 grammes of crystallised manganous sulphate were employed for this purpose, this would correspond to 24·66 grammes of manganese. A solution of ferric citrate is then taken, and the percentage of metallic iron contained therein is determined, for which purpose the iodometric method of assay is both accurate and convenient. If, for example, the iron solution, such as that of the U.S. Pharmacopœia, be found to contain 8 per cent. of metallic iron, 616·5 grammes of it will be required in order to represent 49·3 grammes of iron, an amount corresponding to twice that of the manganese employed.

To the moist manganese citrate, contained in a porcelain dish, is added the solution of ferric citrate, and the mixture heated on a water-bath until complete solution is effected. The liquid is then filtered, evaporated to the consistence of syrup, and spread on plates of glass, so that on drying it may be obtained in the form of scales. It forms handsome yellowish-brown scales, which are readily soluble in water, especially when slightly warmed, affording a clear, yellowish solution. The solution is not precipitated by ammonia, which produces a deep red colour; with potassium ferrocyanide it affords a light blue precipitate, changing to deep blue on the addition of a mineral acid.

The salt may easily be assayed by igniting a portion for the determination of the total mixed oxides, and then in this residue or in a separate portion of the salt determining the iron volumetrically. The amount of metallic iron found is subsequently calculated as Fe_2O_3, the latter deducted from the total amount of oxide, and the remainder, consisting of Mn_3O_4, calculated for the corresponding percentage of manganese.

An example of the remarkable degree of accuracy with which the calculated proportions may be maintained in the finished product, with proper care in the manipulations, is afforded by the following analysis. In a portion of the salt the iron was determined iodometrically as 13·39 per cent. Fe. 0·4520 gramme of the salt gave upon ignition 0·1282 gramme of total mixed oxides. 13·39 per cent. Fe. = 19·13 per cent. Fe_2O_3 or 0·0864 gramme Fe_2O_3. Therefore, 0·1282 – 0·0864 = 0·0418 gramme Mn_3O_4 = 0·03 gramme Mn, or 6·63 per cent. Mn. There was thus found 13·39 per cent. Fe and 6·63 per cent. Mn. When made on a somewhat larger scale the salt ordinarily contains about 14 per cent. of iron and 7 per cent. of manganese.

(3) SOLUBLE IRON AND MANGANESE PHOSPHATE.

This salt is calculated to contain the same relative proportions of iron and manganese as the preceding, and its method of preparation is precisely analogous. Like the so-called Soluble Phosphate of Iron of the U.S. Pharmacopœia, it is really a citro-phosphate. It was prepared in the following manner:—Manganese sulphate, cryst., 100 grammes; sodium phosphate, cryst., 240 grammes; solution of ferric citrate (containing 8 per cent. Fe), 616·5 grammes, or a corresponding amount of solution of other percentage strength.

The salts are dissolved separately in a sufficient amount of water with the aid of heat and filtered. To the solution of manganese sulphate, while warm, is added the warm solution of sodium phosphate. The precipitate of manganese phosphate is allowed to subside, and washed by affusion and decantation with water until the washings afford not more than a very slight reaction for sulphate. The precipitate, while still moist, is then brought into a porcelain dish, the solution of ferric citrate added, and the mixture heated on a water-bath until complete solution is effected. It is then filtered and the liquid spread on glass to scale in the usual manner. The salt should be kept protected from the light.

It forms handsome, greenish-yellow scales, which are slowly soluble in cold, but readily in warm, water, and the solution has the general properties described under Iron and Manganese Citrate. Like the latter, it ordinarily contains about 14 per cent. of iron and 7 per cent. of manganese. The amount of iron contained in the salt may be readily and directly determined by the iodometric method, whilst for the determination of the manganese the usual gravimetric methods for the separation of the two metals must be resorted to, with the consideration of the presence of both citric and phosphoric acids.

In conclusion it may be suggested that, in view of the combined character of these compounds—their ready solubility in water, freedom from objectionable taste, and relative uniformity in the amount of their constituent elements—they would appear to merit favourable consideration and to be well adapted for medicinal use.

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